

Kaempferol: an encouraging flavonoid for COVID-19

[Kaempferol: un flavonoide alentador para COVID-19]

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Recent global pandemic caused by a member of beta-coronaviruses family, SARS-CoV-2, has caused a question of great interest in a wide range of fields. Particularly, finding therapeutic agents has become a central issue to combat COVID-19 disease. Considering the host response and viral load in tissues as two crucial factors for selecting an appropriate molecule, we highlighted probable effect of kaempferol, a plant-derived flavonoid on SARS-CoV-2 infection (Rajendran *et al.*, 2014).

By looking precisely to coronaviruses life cycle in host cell, there are three major serial steps include: virus entry, viral replication, and its release from the host cell. While the two formers are important parts of viral life cycle, the latter one is essential for infection progression. The protein 3a (U274) which is the largest accessory viral channel forming protein and contains 274 amino acids plays a critical role in coronaviral particles release phase (Chien *et al.*, 2013). The formed three transmembrane domain potassium channel is responsible for K⁺ efflux and subsequently, the increased Ca²⁺ concentration in cytoplasm which results in exocytosis of mature virions (Schwarz *et al.*, 2014). In addition to viral release procedure, 3a protein role in caspase-1 activation and its consequent stimulatory effect on NLRP3 inflammasome which are important in IL-1 β secretion and pyroptotic death in lung cells, respectively, was also demonstrated (Yue *et al.*,

2018; Chen *et al.*, 2019).

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one) is a yellow flavonol widely found in several fruits and vegetables of human diet in glycosylated or aglycone form with previously demonstrated antioxidant, anti-inflammatory and antiviral activities (Calderon-Montano *et al.*, 2011). Using *Xenopus* oocyte, 3a protein of SARS-CoV was expressed to evaluate inhibitory effect of kaempferol and its derivatives. Despite significant inhibition of kaempferol on 3a protein, kaempferol glycosides with better solubility exhibited stronger inhibition. Efficacy of all compounds was measured by Ba²⁺-sensitive current. Juglanin, a glycoside of kaempferol with arabinose moiety, potently inhibited 3a protein activity with 2.3 μ M value of IC₅₀ (Schwarz *et al.*, 2014).

There is also a growing body of literature that recognizes the importance of cytokine storm in clinical status of COVID-19 patients. Indeed, non-regulated immune response and further hyperinflammation are responsible for the severity of COVID-19 symptoms (Ye *et al.*, 2020). Restoring encumbered immune status of patients by anti-inflammatory agents is an optimal choice in severe cases. Immunomodulatory effects of kaempferol have been reported by both *in vitro* and *in vivo* investigations and revealed that kaempferol glucorhamnoside could inhibit NF- κ B and MAP kinase phosphorylation. Significant reduction in IL-

1β , IL-6 and TNF- α levels was also observed in an *in vivo* study (Yang *et al.*, 2020; Sun *et al.*, 2019).

Along with this exacerbation in immune response; however, there is increasing concern over oxidative stress which is flared-up consequently. Regarding to this, antioxidant properties of kaempferol reported by Yang *et al.* in lung ischemia-reperfusion injury model with significant superoxide dismutase elevation and decrease in malondialdehyde could additionally confirm previous evidence (Yang

et al., 2020). Figure No. 1 depicted multifactorial beneficial effects of kaempferol briefly.

As 72% of parallelism in 3a protein sequence has been observed between SARS-CoV-2 and SARS-CoV with functional domains conservation (Issa *et al.*, 2020), inhibiting 3a protein by both mutilation of virus release and amelioration in IL-1 β secretion as a pioneer in inflammatory cascade seems to be a promising strategy against SARS-CoV-2.

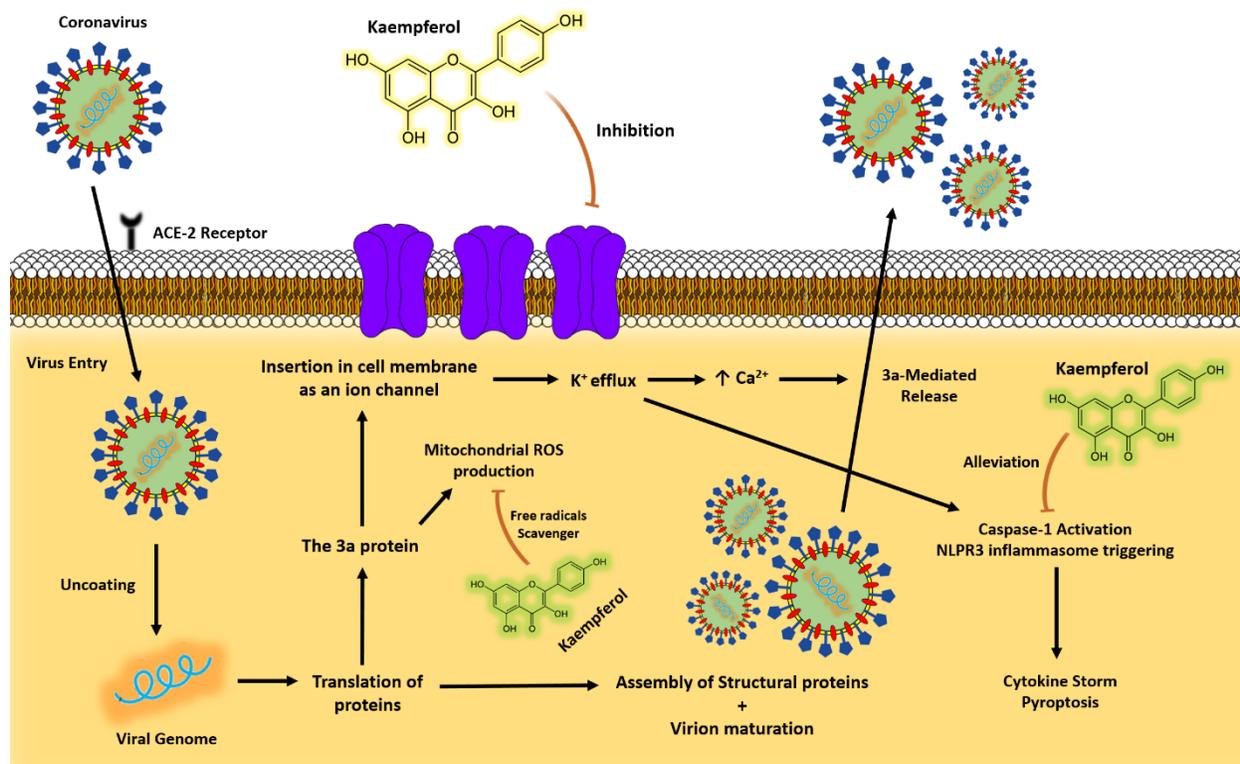


Figure No. 1
Probable beneficial effects of kaempferol in SARS-CoV-2 infection

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